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Original Article

Restrictive fluid resuscitation versus liberal fluid resuscitation in patients with septic shock: comparison of outcomes

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Abstract: Objective: To compare the prognosis of restrictive fluid resuscitation (RFR) versus liberal fluid resuscitation (LFR) in patients with septic shock. Methods: A retrospective analysis was conducted using clinical data from 82 septic shock patients treated in the Intensive Care Unit of Aviation General Hospital from January 2021 to December 2023. Patients were divided into two groups: the LFR group (n=41) and the RFR group (n=41), based on the resuscitation strategy used. Results: Both groups demonstrated significant reductions in heart rate (HR) and significant increases in mean arterial pressure (MAP) and central venous pressure (CVP) post-treatment (all $P < 0.05$). After treatment, the ejection fraction (EF) and cardiac index (CI) were significantly higher in the RFR group compared to the LFR group, while levels of troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were significantly lower in the RFR group (all $P < 0.05$). After treatment, the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores exhibited a marked decrease in both groups, with the RFR group exhibiting greater reductions in both scales compared to the LFR group (both $P < 0.05$). The incidence of complications was significantly lower in the RFR group than in the LFR group ($P < 0.05$). Multivariable analysis identified age and fluid resuscitation modality as risk factors for complications in septic shock. Conclusions: In patients with septic shock, RFR, compared to LFR, appears to better maintain hemodynamic stability and reduce myocardial injury. It also enhances cardiac function, mitigates organ failure, and lowers complication rates, possibly facilitating faster recovery.

Keywords: Septic shock, restrictive fluid resuscitation, liberal fluid resuscitation, organ failure, myocardial function

Introduction

Sepsis refers to a systemic inflammatory response syndrome triggered by infections from bacteria, viruses, or other pathogens. Populations at high risk for sepsis include individuals with impaired immune function, increased exposure to pathogens, and compromised defense barriers [1]. Sepsis typically has an acute onset, with patients presenting with symptoms such as fever, chills, and tachypnea. The condition progresses rapidly, and as the inflammatory response intensifies, the body releases excessive amounts of inflammatory mediators, triggering a cascade that worsens circulatory dysfunction [2]. If not promptly identified, sepsis can progress to severe sepsis (characterized by organ dysfunction and insufficient tissue perfusion) or even septic shock (marked by persistent hypotension and altered consciousness). Patients with septic shock face a high risk of organ failure, poor prognosis, and a significantly increased fatality rate. The diagnosis and treatment of septic shock are central topics in critical care research [3, 4].

The progression of septic shock is closely linked to pathologic processes such as excessive inflammatory response, increased vascular permeability, and coagulation dysfunction. Increased vascular permeability causes capillary leakage, reducing intravascular volume and impairing circulatory volume, which in turn compromises tissue perfusion and oxygen delivery, leading to ischemic and hypoxic injury [5]. The main treatment principles for septic shock

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include infection control and circulatory support. Fluid resuscitation is a cornerstone of circulatory management [6]. The goal of fluid resuscitation is to rapidly restore circulatory volume through the administration of resuscitation fluids. According to the Starling principle, increasing circulatory volume during systemic tissue hypoxia enhances cardiac preload and boosts cardiac output. This corrects hemodynamic abnormalities, restores tissue and organ perfusion, improves oxygen delivery, and prevents further ischemic and hypoxic injury, thereby significantly improving prognosis and reducing mortality [7].

Although existing research supports the importance of fluid resuscitation in septic shock, there is an ongoing debate over the optimal volume of fluid administration. While fluid resuscitation is essential for restoring tissue perfusion, excessive fluid infusion can lead to fluid overload, increasing the risk of pulmonary edema, organ dysfunction, and other complications. This raises challenges in determining the appropriate initial fluid volume and subsequent adjustments [8]. To explore fluid resuscitation strategies in septic shock and provide a reference for later-stage treatment, this study retrospectively analyzed the clinical data of 82 patients with septic shock, categorized by the resuscitation strategies used [liberal fluid resuscitation (LFR) and restrictive fluid resuscitation (RFR)], and compared the prognostic outcomes between the two groups.

Materials and methods

Data sources

The study was reviewed and approved by the Ethics Committee of Aviation General Hospital. This retrospective analysis used data retrieved from the medical record system of the hospital, covering the period from January 2021 to December 2023. The focus was on patients admitted to the intensive care unit (ICU) with septic shock. Informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

Inclusion criteria

Patients were included if they met the following criteria: (1) Diagnosis of septic shock according to the Sepsis 3.0 guidelines by the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) [9]; (2) Aged 18-75 years; (3) Normal immune function; (4) Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 12; (5) Indications for fluid resuscitation and receipt of crystalloid fluid resuscitation therapy.

Exclusion criteria

Patients were excluded if they met any of the following conditions: (1) Cardiovascular or cerebrovascular diseases; (2) Malignant tumors; (3) Time from symptom onset to hospitalization > 3 days; (4) Severe allergic reactions during treatment.

Grouping methods

Both groups received standard treatment, including oxygen therapy, nutritional support, and other basic life-support measures. Venous access was promptly established for subsequent treatment, and bacterial cultures were obtained to identify the infection source. Appropriate anti-infective therapy was administered. Vital signs, including heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP), were closely monitored [9]. Fluid resuscitation therapy was administered using crystalloid fluid (Sodium Chloride Injection, Wuhan Binhu Double Crane Pharmaceutical Co., Ltd., specification: 500 mL, H42020476).

Patients were divided into two groups based on the fluid resuscitation strategy: a LFR group (n=41) and an RFR group (n=41).

LFR Group: Patients in the LFR group received an initial fluid bolus of 1000-1500 mL within the first 60 minutes, aiming to achieve a MAP ≥ 70 mmHg within 6 hours, with a CVP target range of 8-12 mmHg and a urine output goal of 1-1.5 mL/kg/h. If blood pressure remained unstable despite adequate fluid infusion, additional interventions, including fluid supplementation, vasopressors (Norepinephrine Bitartrate Injection, Tianjin Jinyao Amino Acid Co., Ltd., specification: 1 mL: 2 mg, H11020535), and vasodilators, were used to enhance tissue perfusion [10].

RFR Group: Patients in the RFR group initially received 500-1000 mL of fluid within the first 60 minutes. Once a MAP of 50-60 mmHg was achieved and urine output reached 0.5-1 mL/kg/h, the fluid infusion rate was reduced. Subsequent fluid administration was limited to less than 3000 mL/day, with the MAP maintained at approximately 50 mmHg [7].

Data collection

General clinical data, including sex, age, and the cause of septic shock, were extracted from the medical record system. The following treatment indicators were recorded: (1) Treatment outcomes: The fluid infusion volume, ICU length of stay, and 28-day all-cause mortality were recorded for both patient groups [8]; (2) Hemodynamic indicators: HR, MAP, and CVP were recorded for both groups before and after treatment [2]; (3) Cardiac and myocardial function indicators: Echocardiography was performed to assess the ejection fraction (EF) and cardiac index (CI) before and after treatment. Venous blood samples were collected, and plasma was separated at the corresponding time points. Plasma levels of troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured using a fully automated biochemistry analyzer (SD1, Seamaty) [7]; (4) Condition and organ failure status: The Acute Physiology and Chronic Health Evaluation II (APACHE II) [10] and Sequential Organ Failure Assessment (SOFA) [7] scores were recorded before and after treatment. The APACHE II score includes acute physiology (0-48 points), age (0-6 points), and chronic health (2-5 points), with a total score range of 0-71 points. Higher scores indicate more severe conditions. The SOFA score, proposed by the European Society of Intensive Care Medicine, uses objective continuous variables to assess the occurrence, progression, and risk of multiple organ dysfunction syndrome (MODS). It includes the assessment of six organ systems: respiratory, hematologic, liver, cardiovascular, central nervous, and renal, with scores ranging from 0 to 4 for each organ, and a total score from 0 to 24. Higher scores indicate worse organ function and poorer prognosis [11]; (5) Complications: The occurrence of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), MODS, and acute renal failure (ARF) during treatment was recorded for both groups of patients [12].

Statistical methods

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0. Counted data were expressed as percentages (%), while continuous data with a normal distribution were presented as mean ± standard deviation (mean ± SD). Intergroup comparisons were performed using χ^2 and t-tests for counted data and continuous data, respectively. Intragroup comparisons before and after treatment were performed using repeated-measures analysis of variance (ANOVA). Multivariable logistic regression was used to identify factors influencing the prognosis of patients with septic shock. A *P* value of < 0.05 was considered significant.

Results

Comparison of general clinical data

After screening, 113 patients with septic shock were initially included. Of these, 2 were excluded due to being under 18 years of age, 2 due to epilepsy during treatment, 4 due to withdrawal from treatment, 4 due to a hospitalization duration greater than 3 days, 8 due to concurrent malignancies, and 11 due to APACHE II scores below 12. A total of 82 patients with septic shock were ultimately included in the study. Based on different fluid resuscitation strategies, patients were divided into the LFR group (n=41) and the RFR group (n=41) (**Figure 1**). The baseline data of the two groups, including sex, age, and causes of septic shock, showed no significant differences (all $P > 0.05$), indicating good comparability (**Table 1**).

Comparison of treatment outcome

The fluid infusion volume and ICU length of stay in the RFR group were significantly lower than those of the LFR group (both $P < 0.05$), indicating that RFR reduced the volume of fluid administered and shortened ICU stay in patients with septic shock. The 28-day all-cause mortality rate in the RFR group (4 cases, 9.76%) was not significantly different from that in the LFR group (6 cases, 14.63%) ($P > 0.05$, **Figure 2**).

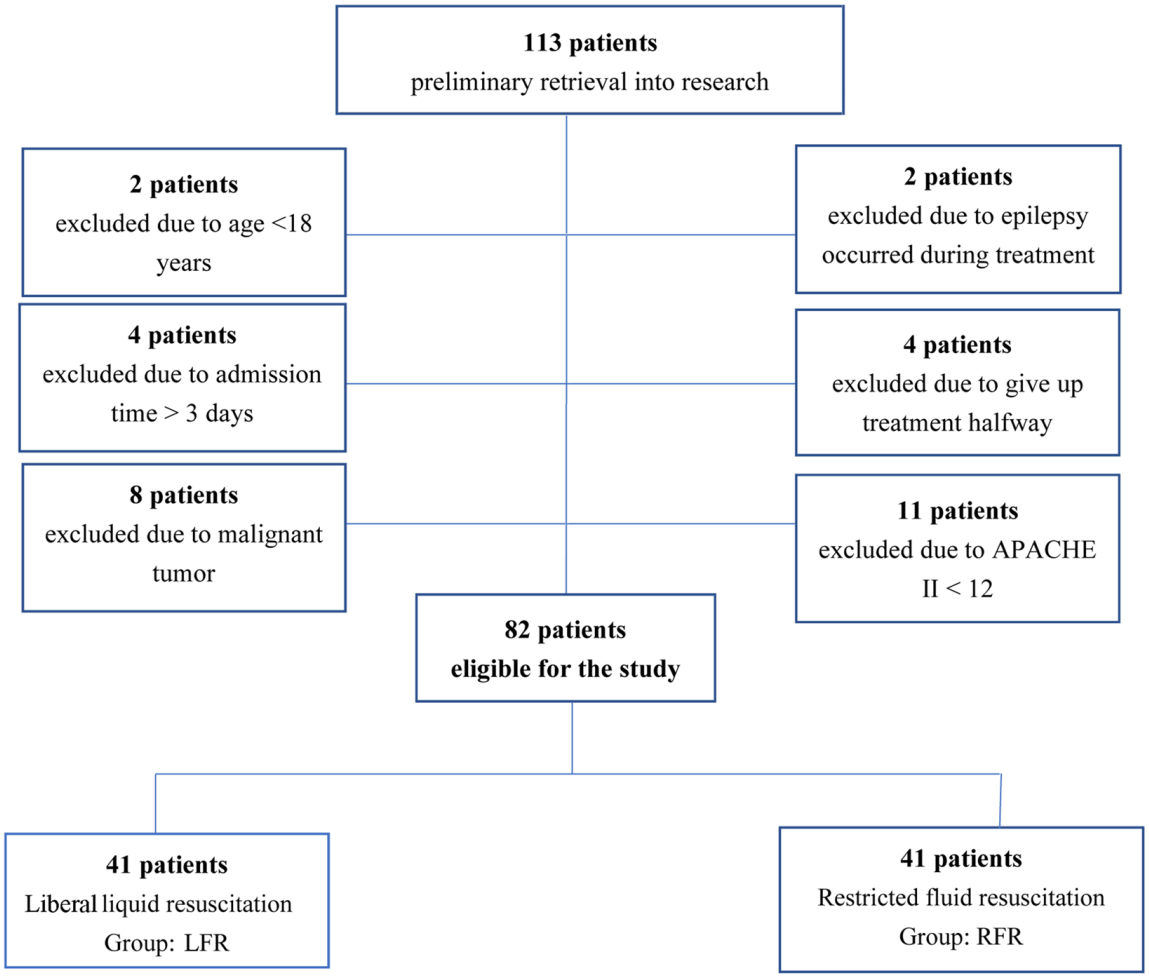

Figure 1. Flow chart for screening and grouping of septic shock cases. LFR: liberal fluid resuscitation; RFR: restrictive fluid resuscitation; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 1. Comparison of general clinical data between the two groups ($\bar{x} \pm s$)/[n (%)]

Data		LFR (n=41)	RFR (n=41)	t/χ^2	*P*
Sex (men/women)		26/15	24/17	0.651	0.205
Age (years)		56.56±12.07	56.24±9.79	3.590	0.062
Etiology	Severe pneumonia	15	16	0.209	0.901
	(Abdominal/urinary tract) infections	18	16		
	Trauma	8	9		
ASA classification	ASA I-II	30	31	0.577	0.449
	ASA III-IV	11	10		
Underlying diseases	Hypertension	22	19	0.118	0.906
	Diabetes	6	8	0.971	0.332
	Coronary heart disease	3	5	0.632	0.811
	Chronic obstructive pulmonary disease	1	0	0.602	0.625
	Chronic kidney disease	3	2	0.135	0.958

Note: LFR, liberal fluid resuscitation; RFR, restrictive fluid resuscitation; ASA, American Society of Anesthesiologists.

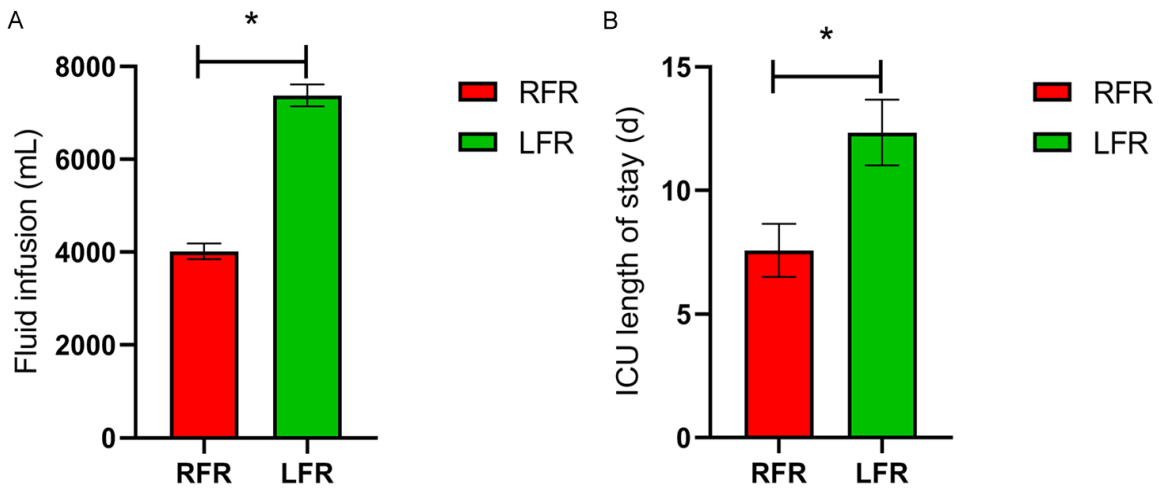

Figure 2. Comparison of the fluid infusion volume and ICU length of stay between the two groups. The fluid infusion volume (A) and ICU length of stay (B) in the RFR group were significantly lower than those of the LFR group ($P < 0.05$). LFR: liberal fluid resuscitation; RFR: restrictive fluid resuscitation; ICU: intensive care unit. * indicates significant difference between groups.

Comparison of hemodynamic indicators before and after treatment

Before treatment, there were no significant differences in HR, MAP, or CVP between the two groups (all P > 0.05). After treatment, HR decreased significantly, while MAP and CVP increased significantly in both groups compared to baseline (all P < 0.05). However, no significant differences were observed between the groups in these indicators after treatment (P > 0.05), suggesting that both RFR and LFR improved hemodynamic readings in the patients (**Figure 3**).

Comparison of cardiac and myocardial function indicators before and after treatment

Before treatment, there were no significant differences in EF, CI, or plasma levels of cTnI and NT-proBNP between the two groups (all P > 0.05). After treatment, both groups showed significant increases in EF and CI, with the RFR group showing significantly greater improvements in both EF and CI compared to the LFR group (both P < 0.05). Both groups also exhibited significant reductions in plasma levels of cTnI and NT-proBNP after treatment, with the RFR group showing a significantly greater decrease in these biomarkers than the LFR group (both P < 0.05) (**Table 2**).

Comparison of condition and organ failure status between the two groups before and after treatment

Before treatment, no significant differences were observed in the APACHE II and SOFA scale scores between the two groups (both P > 0.05). After treatment, both groups showed significant reductions in their APACHE II and SOFA scores, with the RFR group showing a greater decrease (both P < 0.05, **Figure 4**).

Comparison of incidence of complications

The incidence of complications in the RFR group (14.43%) was significantly lower than in the LFR group (34.15%) (P < 0.05) (**Table 3**).

Comparison of risk factors for complications of septic shock

Univariate analysis revealed that age, etiology, and fluid resuscitation modality were risk factors for complications in septic shock. A multivariable logistic regression analysis was performed with the presence or absence of complications as the dependent variable (presence = 0, absence = 1), and the statistically significant factors from the univariate analysis (age, etiology, and fluid resuscitation modality) as independent variables (**Tables 4**, **5**).

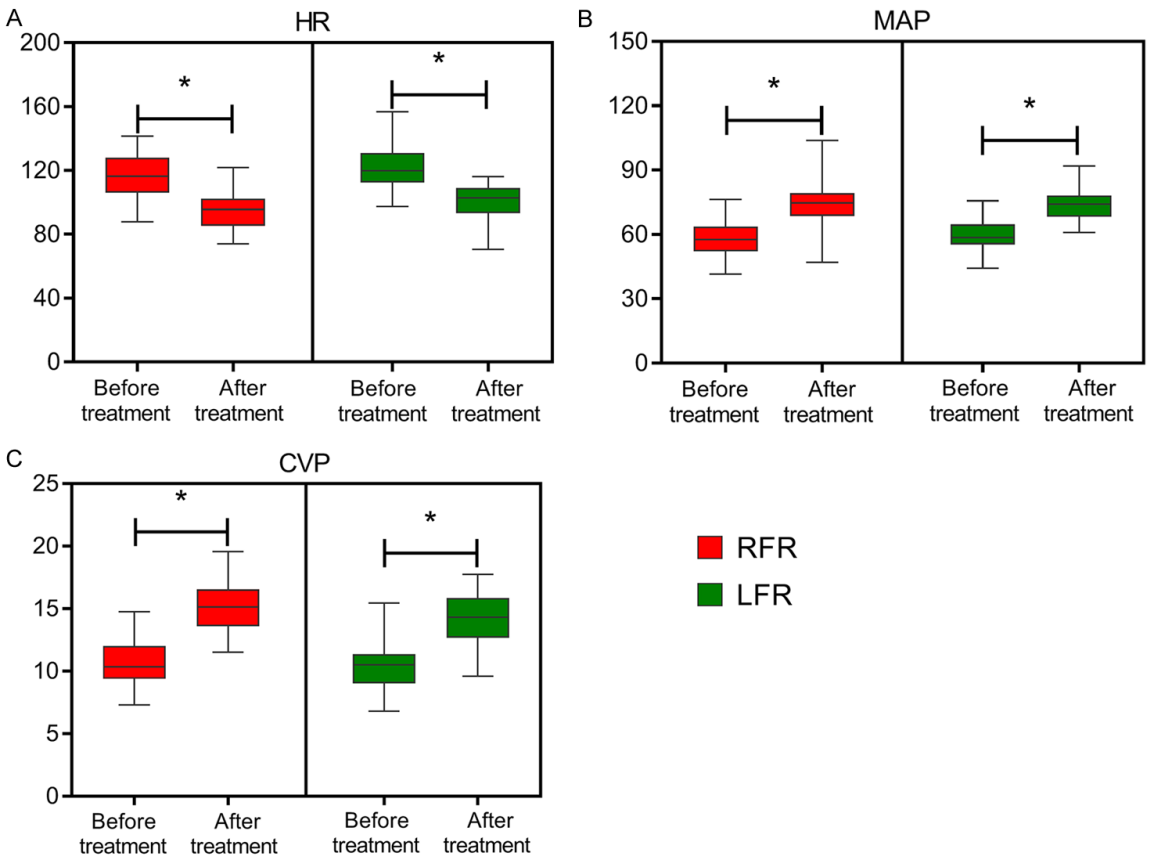

Figure 3. Comparison of the hemodynamic indicators between the two groups before and after treatment. Before treatment, there were no significant differences in HR, MAP, or CVP between the two groups ($P > 0.05$). After treatment, HR (A) decreased significantly, while MAP (B) and CVP (C) increased significantly in both groups compared to before treatment ($P < 0.05$). After treatment, there were no significant differences in HR, MAP, or CVP between the two groups ($P > 0.05$). LFR: liberal fluid resuscitation; RFR: restrictive fluid resuscitation; HR: heart rate; MAP: mean arterial pressure; CVP: central venous pressure. * indicates significant difference between groups.

Table 2. Comparison of the cardiac and myocardial function indicators between the two groups before and after treatment ($\bar{x} \pm s$)

Group	Time	EF (%)	CI (L/min/m^2)	cTnI (×10^{-2} μg/L)	NT-proBNP (ng/L)
RFR	Before treatment	36.53±10.25	3.83±1.16	1.60±0.38	1683.67±419.56
	After treatment	48.03±8.26	5.04±1.36	1.11±0.25	960.35±236.59
LFR	Before treatment	36.39±10.05*	3.85±1.22*	1.58±0.37*	1606.84±408.95*
	After treatment	41.71±8.33$^\#$	4.17±1.29$^\#$	1.29±0.30$^\#$	1323.57±298.62$^\#$
t^*	-	0.062	0.076	0.241	0.840
P^*	-	0.950	0.940	0.810	0.404
$t^\#$	-	3.450	2.972	2.951	6.105
$P^\#$	-	< 0.001	0.004	0.004	< 0.001

Note: LFR, liberal fluid resuscitation; RFR, restrictive fluid resuscitation; EF, ejection fraction; CI, cardiac index; cTnI, troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide. t^* and P^* denote intergroup comparisons before treatment; $t^\#$ and $P^\#$ denote intergroup comparisons after treatment.

Discussion

An analysis of the Global Burden of Disease Study 2020 reported that, in 2017, there were 48.9 million cases of sepsis globally, with approximately 25% of these cases resulting in sepsis-related death, accounting for about 19% of all global deaths. Sepsis continues to pose a

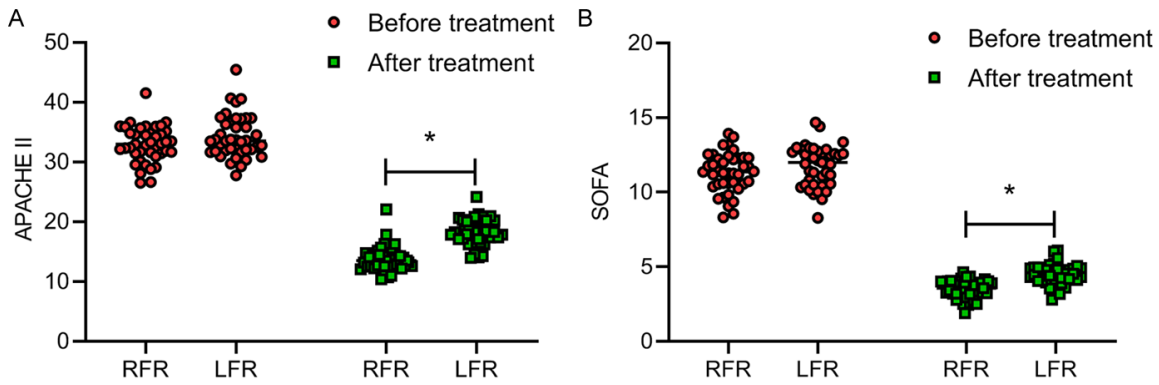

Figure 4. Comparison of condition and organ failure status between the two groups before and after treatment. There were no significant differences in the APACHE II or SOFA scale scores between the two groups before treatment ($P > 0.05$). After treatment, the APACHE II (A) and SOFA scale (B) scores significantly decreased in both groups, and were much lower in the RFR group ($P < 0.05$). LFR: liberal fluid resuscitation; RFR: restrictive fluid resuscitation; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment. * indicates significant difference between groups.

Table 3. Comparison of the incidence of complications between the two groups [n (%)]

Group	Number of cases	ARDS	DIC	MODS	ARF	Incidence
RFR	41	2 (4.88)	1 (2.44)	2 (4.88)	1 (2.44)	6 (14.43)
LFR	41	4 (9.76)	3 (7.32)	5 (12.20)	2 (4.88)	14 (34.15)
χ^2	-	-	-	-	-	4.232
P	-	-	-	-	-	0.040

Note: LFR, liberal fluid resuscitation; RFR, restrictive fluid resuscitation; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; ARF, acute renal failure.

significant threat to human life and places a substantial burden on global health systems [13]. Septic shock develops as a consequence of the progression and poor control of sepsis. The body succumbs to dysregulation of the systemic inflammatory response triggered by microbial pathogens, such as bacteria and fungi. The extensive release of inflammatory mediators damages blood vessels, leading to inadequate tissue perfusion and fatal organ dysfunction [14]. Patients with septic shock often exhibit symptoms such as impaired consciousness, oliguria, and anuria, which are common critical conditions in the ICU, characterized by rapid progression and high mortality rates. Infants, the elderly, and individuals with severe trauma or compromised immune systems are at higher risk for septic shock [15].

Currently, the treatment of septic shock primarily involves three main strategies: infection control, stabilization of hemodynamics, and symptomatic supportive therapy [16]. Early identification of the infection source and timely administration of anti-infective agents are essential for treating septic shock. Symptomatic supportive therapy is crucial for preventing the condition from worsening, while fluid resuscitation and hemodynamic stabilization play a pivotal role in management [17]. Early anti-infective therapy and fluid resuscitation are strongly recommended for patients with septic shock, since they are beneficial in improving outcome. However, there remains ongoing debate regarding whether RFR or LFR should be implemented [18].

Research has shown that while LFR can maintain a patient's "adequate volume" status, it carries risks [8]. LFR typically involves infusing 50-75 mL/kg of fluid within the first 6 hours of resuscitation, followed by adjustments to vasopressor therapy based on clinical conditions [19]. Perez et al. [20] highlighted that LFR in critically ill patients may lead to fluid overload, thereby increasing the risk of mortality. As a result, an RFR strategy is often recommended. This is supported by Shapiro et al. [21], who found that RFR not only reduces the total volume of fluid administered but also does not increase the 90-day mortality rate or the incidence of severe adverse reactions. Munroe et

Table 4. Univariate analysis of the risk of septic shock complications [n (%)]

Category		n	Incidence of complications	t/χ^2	*P*
Sex	Men	50	12 (24.00)	0.011	0.918
	Women	32	8 (25.00)		
Age	18-39	13	2 (15.38)	5.523	0.041
	40-60	45	8 (17.78)		
	> 60	24	10 (41.67)		
Etiology	Severe pneumonia	31	5 (16.13)	6.151	0.046
	(Abdominal/urinary tract) infections	34	7 (20.59)		
	Trauma	17	8 (47.06)		
Fluid resuscitation modalities	RFR	41	6 (14.43)	4.232	0.040
	LFR	41	14 (34.15)		

LFR, liberal fluid resuscitation; RFR, restrictive fluid resuscitation.

Table 5. Multivariable analysis of risk factors for septic shock complications

Risk factor	β	SD	Wald	*P*
Age	0.911	0.192	20.402	0.010
Fluid resuscitation modalities	-0.506	0.197	6.653	0.008

SD, standard deviation.

al. [22] further emphasized that, due to the adverse effects of excessive fluid infusion, fluid resuscitation practices are now shifting toward low-volume strategies, underscoring the importance of early vasopressor administration. These findings suggest that excessive fluid infusion may exacerbate tissue edema, particularly when the lymphatic system is overwhelmed, increasing the likelihood of fluid retention.

In this study, we retrospectively analyzed the clinical data of 82 patients with septic shock. The results showed that the RFR group required significantly less fluid infusion and had a shorter ICU length of stay compared to the LFR group. However, there was no significant difference in the 28-day all-cause case fatality rate between the two groups (P > 0.05). This finding aligns with Reynolds et al.'s [23] systematic review and meta-analysis, which similarly concluded that RFR did not increase mortality.

Regarding hemodynamic changes in sepsis, Daulasim et al. [24] emphasized that patients with sepsis require increased circulatory volume to maintain adequate blood perfusion due to impaired vascular tone. Yajnik and Maarouf [25] reported that sepsis induces endothelial cell damage, disrupts the interaction between endothelial cells and pericytes, and impairs vascular barrier function. Jiang et al. [26] further confirmed that such injury increases capillary permeability and reduces intravascular volume. In our study, both resuscitation strategies led to significant reductions in HR and a marked increase in MAP and CVP, with no significant differences between the groups. These findings are consistent with those of Sankar et al. [27], who demonstrated that appropriate intravenous fluid administration can rapidly improve circulatory conditions.

Regarding the use of vasoactive drugs, Russell et al. [28] highlighted that norepinephrine, as both a α- and β-adrenergic agonist, plays a crucial role in enhancing vasoconstriction and improving cardiac perfusion.

Our study also showed that after treatment, both groups exhibited significantly elevated EF and CI, with the increases in EF and CI being greater in the RFR group than in the LFR group. Additionally, plasma levels of cTnI and NT-proBNP decreased significantly in both groups, with the reductions in the RFR group being greater than those in the LFR group. This suggests that RFR can improve cardiac function and reduce myocardial injury. During septic shock, the systemic inflammatory response leads to the secretion of a large number of

inflammatory mediators, which can damage the cardiovascular system. Reactive oxygen species generated through complex reactions after the activation of endothelial cells and neutrophils can induce myocardial damage and trigger a cascade of inflammatory responses, accelerating myocardial cell death [29]. RFR improves organ tissue perfusion, reduces tissue hypoxia and acidosis, and alleviates myocardial injury. Furthermore, reduced fluid infusion helps minimize organ edema, lowers the organ burden, and enhances cardiac function [30]. The primary goal of fluid resuscitation is to correct tissue hypoperfusion and restore tissue oxygenation [31].

In this study, both APACHE II and SOFA scores significantly decreased in both groups after treatment, with the RFR group showing significantly lower scores than the LFR group. The incidence of complications in the RFR group was also significantly lower than that of the LFR group. These findings suggest that RFR has a beneficial therapeutic effect on septic shock and reduces the likelihood of complications, which aligns with the results reported by Zhou et al. [32]. A likely explanation is that RFR reduces the fluid load on the body during the later stages of resuscitation, accelerates the balance of internal circulation, facilitates recovery, and lowers the risks of ARDS, DIC, MODS, and ARF [15].

The innovation of this study lies in its comprehensive evaluation, extending beyond traditional prognostic indicators such as 28-day case fatality and ICU length of stay. It systematically assessed hemodynamic data, cardiac and myocardial function indicators, and APACHE II scores, with a particular focus on the impact of RFR on cardiac function. Notably, the RFR group exhibited superior improvements in EF and CI, as well as greater reductions in cTnI and NT-proBNP levels compared to the LFR group. These findings provide a new reference for the clinical selection of fluid resuscitation strategies and offer stronger evidence-based support for the application of RFR in clinical practice.

This study primarily analyzed the prognostic outcomes of RFR and LFR. However, the limited sample size may affect the accuracy and generalizability of some results. Furthermore, while the study compared the effects of the two resuscitation strategies on complications, it did not delve deeply into the underlying mechanisms. Further research is needed to address this limitation. Additionally, the study did not stratify or compare the therapeutic efficacy of LFR and RFR for sepsis of different etiologies (e.g., trauma vs. infection), which should be explored in future studies.

In conclusion, in the treatment of septic shock, RFR, compared to LFR, can maintain hemodynamic stability while alleviating myocardial injury. This approach can enhance cardiac function, mitigate organ failure, and reduce the incidence of complications, ultimately promoting patient recovery.

Disclosure of conflict of interest

None.

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